Comments to the NTP Board of Scientific Counselors' Report on Carcinogens Subcommittee October 30-31, 1997

We note that "strong inorganic acid mists containing sulfuric acid" is nominated for listing as "known to be a human carcinogen". We believe the evidence clearly does not support such a listing.

Sulfuric acid mist has been studied as a potential carcinogen in three life-time animal studies sponsored by US Government agencies. Studies in hamsters, guinea pigs, and rats at high doses for the life of the animals were all negative.

There are some epidemiology studies that suggest an association between exposure to strong inorganic acid mists and cancer of the larynx. However, there are major inconsistencies between studies of the same design, dose-response comparisons between and within studies do not support a causal relationship, exposure assessment in all studies was inadequate and was not even measured in most studies, and control of confounding variables when attempted was inadequate. We intend to demonstrate that the evidence for carcinogenicity is best characterized as inadequate. In our view the evidence does not rise to the level of "limited" and clearly does not approach the level of "sufficient".

We will review the three key studies considered by the International Agency for Research on Cancer (IARC) and demonstrate serious problems with consistency, dose response, exposure assessment, and confounding variables.

A 1984 case-control study by Soskolne, et al. reported a strong dose-response relationship between exposure to sulfuric acid mist and cancer of the larynx. However, this strong positive dose-response relationship was found only when using a non-conventional dose category called "mean grade". A subsequent reanalysis of this same data by Suarez-Almazor, et al. reported a negative dose-response when using a cumulative or total dose as the exposure category. The odds ratios for this reanalysis were 1.0, 0.58, and 0.70 for the "no/low", "medium", and "high" exposure categories.

A second case-control study by Soskolne, et al. also demonstrated an apparent positive dose-response between possible exposure to sulfuric acid and cancer of the larynx. A major problem with this study was the lack of any direct questions on sulfuric acid exposure to the cases or controls. Possible exposure to sulfuric acid was ranked by one of the authors based on job title, industry and era. The overall rankings of possible exposure among both cases (72.7%) and controls (51.4%) are inconsistent with other similar studies and are so high as to be unbelievable. In addition, a similar case-control study by Brown, et al. was negative.

A cohort study by Steenland, et al. reported a Standardized Incidence Ratio (SIR) of 2.6 for cancer of the larynx in a study of workers employed in metal pickling. In a critical review of epidemiologic studies, Sathiakumar, et al. found that this study was of questionable validity for the following reasons: selection bias; confounding by smoking and alcohol use; and lack of positive dose-response when considering time since first exposure. It should be noted that the average exposure to sulfuric acid mist was reported as 0.2 mg/m^3.

The results of this study are in marked contrast to a 1996 study by Coggan, et al. In the Coggan study there was no excess risk of mortality for cancers of the lung, larynx, or nasopharnyx. In fact the Standardized Mortality Ratio (SMR) for cancer of the larynx was 0.48 among those definitely exposed to sulfuric acid mist. Only one additional living case of cancer of the larynx was identified through a search for living cases. Given the high cure rate for this cancer the SIR would be even lower than the SMR of 0.48. In this study exposures for most of the workers was reported as above 1.0 mg/m^3. Given this higher exposure one would have expected a much higher risk of cancer of the larynx than that reported in the Steenland, et al. study. Such a result was not seen, in fact, the results were a negative SMR.

In summary, we believe we have demonstrated that all the key epidemiology studies relied upon by IARC are seriously flawed. These studies are either inconsistent with other studies using similar methodologies, or inconsistent with subsequent more appropriate reanalysis of their own data, or have exposure assessment problems that render the studies unreliable. We urge the subcommittee to carefully review our more detailed written comments. We believe that after a thorough review the subcommittee would have to conclude that the evidence is insufficient to list "strong inorganic acid mists containing sulfuric acid" as "known to be a human carcinogen". Eventhough there are some positive associations reported in the scientific literature between sulfuric acid mist exposure and cancer of the larynx we believe that the evidence when viewed in its entirety is best characterized as inadequate as opposed to limited. The evidence is clearly not "sufficient".

Comments from the Chemical Manufacturer's Association Panel on Inorganic Acid Mists

by

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The evidence does not support the listing of strong inorganic acid mists containing sulfuric acid

- Sulfuric acid mist is negative in lifetime studies in three animal species.
- The results of epidemiology studies are inconsistent, confounding was not controlled, exposures were not quantified and were often not even confirmed, and dose-response usually did not correlate with surrogates of exposure.

All key studies are seriously flawed

- A reanalysis of Sosklone's 1984 study showed a negative dose response when using cumulative dose.
- Soskolne's geographical study in Southern Ontario had unrealistically high estimates of exposure and is inconsistent with the Brown study in Texas.

All key studies are seriously flawed

- Steenland's laryngeal cancer incidence study is seriously flawed and the results were not replicated in the 1996 Coggan study which had an SMR for cancer of the larynx of 0.48.

Summary

- All key studies are seriously flawed.
- Other similar studies or reanalyses are negative for cancer of the larynx.
- All animal studies are negative.
- The body of evidence is best characterized as inadequate.